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(54) Title: A PROCESS FOR PRODUCING 3,4-DIHYDRO NAPHTHYRIDINONE ANALOGS

(57) Abstract: This invention is to provide a process for producing 3,4-dihydro naphthyridinone analogs and salts thereof containing the structure shown by the following structural formula (I).The naphthyridinone analogs with an electrowithdrawing group in 3-position are easily converted to corresponding 3,4-dihydro naphthyridinone analogs in the presence of reductant, e.g. sodium borohydride and lithium borohydride. The reduction can be performed in mild condition, and the intermediate naphthyridinone analogs containing the structure shown by the following structural formula (II) can be prepared easily under mild condition too, so various substituent can be introduced to the 3,4-dihydro naphthyridinone analogs.

A PROCESS FOR PRODUCING 3,4-DIHYDRO NAPHTHYRIDINONE ANALOGS

TECHNICAL FIELD

The present invention relates to novel synthetic method of 3,4-dihydro naphthyridinone analogs. The compound can be used, e.g. as a pharmaceutical intermediate of pyridine derivatives which inhibit IκB kinase β (IKK-β or IKK-beta) activity, thus inhibit nuclear factor kappa B (NF-κB) activity, and can be used for the prophylaxis and treatment of diseases associated with NF-κB activity, in particular for the treatment of inflammatory diseases.

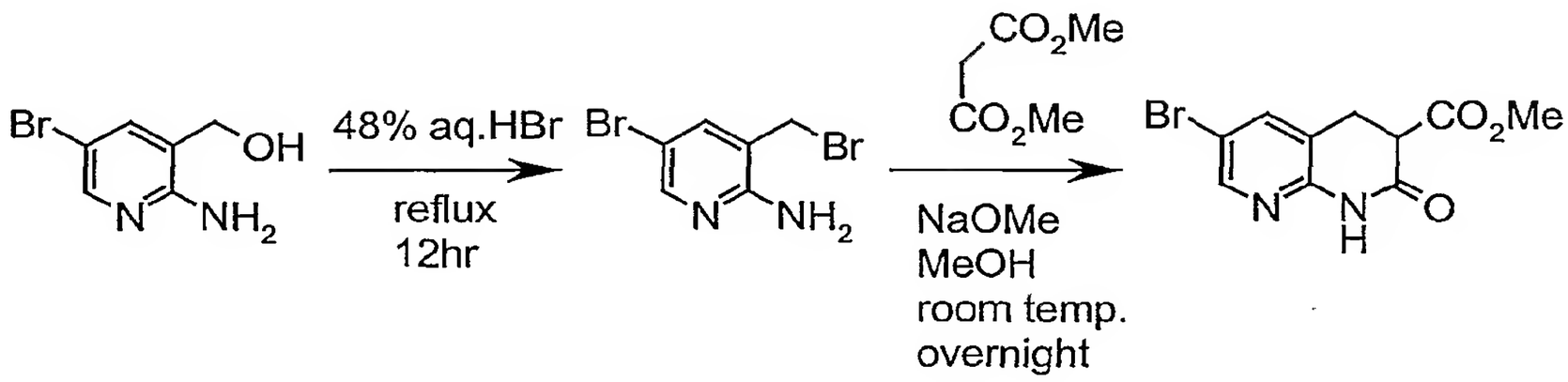
BACKGROUND ART

Nuclear factor kappa B (NF-κB) belongs to a family of closely related homo-and hetero-dimeric transcription factor complexes composed of various combinations of the Rel/NF-κB family of polypeptides. NF-κB and related family members are involved in the regulation of more than 50 genes relating to immune and inflammatory responses ((Barnes PJ, Karin M, N. Engl. J. Med. 336, 1066-1071(1997)) and (Baeuerle PA, Baichwal VR, Adv. Immunol. 65, 111-137 (1997)).

The development of a novel compound having effective anti-inflammatory actions based on a specific and selective inhibitory activity to NF-κB has been desired.

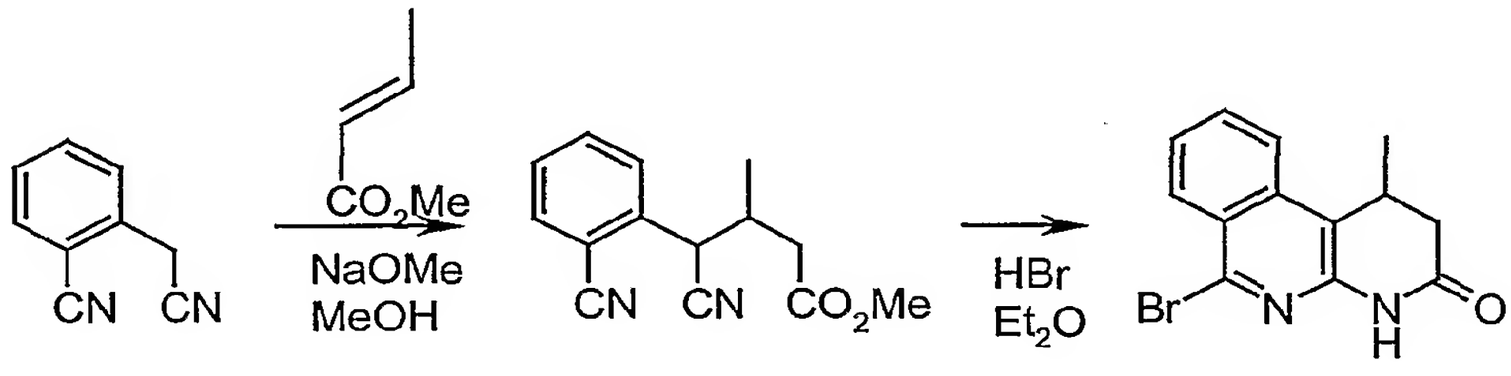
The present inventor has found that 3,4-dihydro naphthyridinone analogs are useful for intermediate of the novel compound. Synthetic method of 3,4-dihydro naphthyridinone analogs shown by the following Scheme 1 is disclosed in WO 2001027103. But the intermediate bromomethyl compound is prepared under strongly acidic condition, so it is difficult to introduce acid-sensitive groups in 3,4-dihydro naphthyridinone analogs.

Scheme 1



Moreover, another synthetic method of 3,4-dihydro naphthyridinone analogs such as shown by the following Scheme 2 is disclosed in DE 3423003 and Al 19860102,but the reaction is performed under strongly acidic condition and the derivation of 3,4-dihydro naphthyridinone analogs is very limited too.

Scheme 2



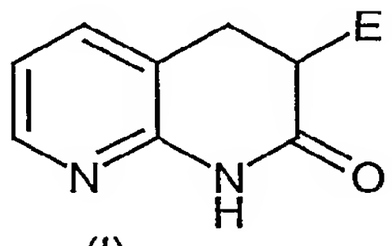
DISCLOSURE OF INVENTION

The object of this invention is to provide the synthetic method that can prepare 3,4-dihydro naphthyridinone analogs with various substituents in mild conditions.

As a result of extensive studies on chemical modification of source materials, the present inventor has found that naphthyridinone analogs with an electrowithdrawing group in 3-position are easily converted to corresponding 3,4-dihydro naphthyridinone analogs in the presence of reductant, e.g. sodium borohydride and lithium borohydride. The reduction can be performed in mild condition, and the intermediate naphthyridinone analogs can be prepared easily under mild condition

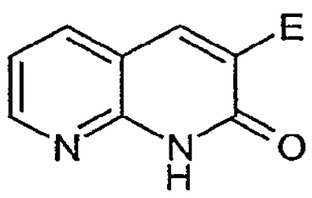
too, so various substituent can be introduced to the 3,4-dihydro naphthyridinone analogs. The present invention has been accomplished based on these findings.

This invention is to provide A process for producing 3,4-dihydro naphthyridinone analogs and salts thereof containing the structure shown by the following structural formula (I);



(I)

comprising the reduction of naphthyridinone analogs containing the structure shown by the following structural formula (II);

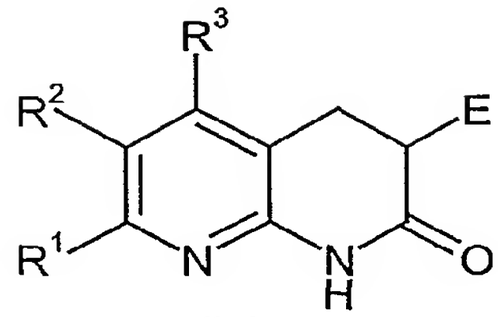


(II)

wherein E is an electrowithdrawing group.

The preferable electrowithdrawing group is carbamoyl, cyano,carboxyl, C_{1-6} alkoxy-carbonyl, C_{1-6} alkylcarbamoyl, nitro, C_{1-6} alkylsulfonyl, aryl sulfonyl, or aryl-carbamoyl.

The preferable structure of the 3,4-dihydro naphthyridinone analogs is shown by the following structural formula (Ia);

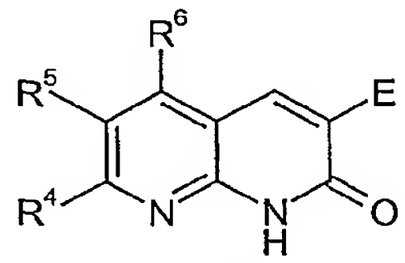


(Ia)

wherein:

R^1 , R^2 and R^3 are different or identical and represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, carboxyl, halogen, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, halogen substituted alkyl, nitro, cyano, hydroxy, aryl, heteroaryl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{3-8} cycloalkylamino, benzylamino, carbamoyl, -O-C_{1-6} alkylene-phenyl, -O-phenyl, styryl or 1,2,3,6-tetrahydro-pyridine, and optionally substituted by one or more substituents;

and the preferable structure of the naphthyridinone analogs are shown by the following structural formula (IIa);



(IIa)

wherein R^4 to R^6 are the same as R^1 to R^3 defined above or the groups which can be reduced to R^1 to R^3;

E is carbamoyl, cyano, carboxyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbamoyl, nitro, C_{1-6} alkylsulfonyl, aryl sulfonyl, or arylcarbamoyl.

The more preferable compound of the formula (Ia) and (IIa) are those wherein;

R^1 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, carboxyl, halogen, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, halogen substituted alkyl, nitro, cyano, hydroxy, phenyl, 2-

pyridil, 3-pyridil, 4-pyridil, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, amino, C_{1-6} alkylamino, C_{3-8} cycloalkylamino, benzylamino, carbamoyl, -O-C_{1-6} alkylene-phenyl, or -O-phenyl, and R^1 is optionally substituted by one or more substituents,

wherein the optional substituents are each independently hydrogen, C_{1-6} alkyl, halogen, hydroxy, C_{1-12} alkoxy, nitro, amino, C_{1-6} alkylsulfonylamino, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, di (C_{1-6} alkyl)amino, C_{1-6} alkanoylamino, phenyl C_{1-6} alkylamino, phenylsulfonylamino, or -O-$(CH_2)_n$-R^{11},

wherein n represents an integer selected from 0 to 6, and R^{11} is C_{2-6} alkenyl, benzoyl, diphenylmethyl, di (C_{1-6} alkyl)amino, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, or a 3 to 10 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group consisting of S, O and N as heteroatoms and is optionally substituted by C_{1-6} alkyl, mono or di halogen, halogen substituted C_{1-6} alkyl, nitro, ciano, C_{1-6} alkoxycarbonyl, phenyl, hydroxy, amino, C_{1-6} alkylamino, di (C_{1-6} alkyl)amino, C_{1-6} alkanoylamino, C_{1-6} alkoxy, or carbamoyl;

R^2 is hydrogen, hydroxy, halogen, or C_{1-6} alkyl;

R^3 is 1,2,3,6-tetrahydro-pyridine, optionally substituted phenyl or styryl;

wherein the optional substituents are each independently hydrogen, halogen, amino, C_{1-6} alkoxy, di C_{1-6} alkylamino, C_{1-6} alkanoylamino, C_{1-6} alkyl(hydroxy C_{1-6} alkyl)amino, C_{1-6} alkyl(benzyl)amino, morpholino, optionally substituted piperidino, or optionally substituted pyrrolidino, C_{1-6} alkylsulfonylamino, piperidino-C_{1-6} alkylene-oxy, -CO-NHR^{51}, or –NH-COR^{51},

wherein R^{51} represents piperidino-C_{1-6} alkylene, carboxy-C_{1-6} alkylene, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6} alkylene, oxotetra-

hydrofuryl, oxopyrrolidinyl, $-CH(OH)R^{51a}$, $-CH(NH_2)R^{51b}$, $-C_{1-6}$ alkylene-R^{51c},

wherein R^{51a} is carboxy-C_{1-6} alkylene or C_{1-6} alkoxycarbonyl-C_{1-6} alkylene,

R^{51b} is C_{1-6} alkyl, or carboxy-C_{1-6} alkylene,

R^{51c} is optionally substituted piperidino, optionally substituted piperazino, optionally substituted amino, or $-CH(NH_2)$-carboxy;

$-CR^{31}R^{32}R^{33}$,

wherein R^{31} is hydrogen or C_{1-6} alkyl,

R^{32} is hydrogen, α-aminobenzyl, a 5 to 8 membered saturated ring having 0 to 3 atoms selected from the group consisting of S, O and N as heteroatoms, or optionally substituted C_{1-6} alkyl, and

R^{33} is hydrogen, amino, C_{1-6} alkoxycarbonylamino, C_{2-6} alkenyloxy-carbonylamino, piperidino-C_{1-6} alkylcarbonylamino, or 9-fluorenyloxycarbonylamino or

R^{32} and R^{33} may form, together with the adjacent carbon atom, an optionally substituted or optionally benzene fused 5 to 8 membered saturated ring having 0 to 3 heteroatoms selected from the group consisting of N, O and S as heteroatoms;

$-NR^{34}R^{35}$,

wherein R^{34} is hydrogen or C_{1-6} alkyl and R^{35} is hydrogen, C_{1-6} alkyl, or a 5 to 8 membered saturated ring having 0 to 3 hetero-atoms selected from the group consisting of N, O and S as heteroatoms, or $-(CH_2)_m-NR^{351}R^{352}$(m represents any of integers from 1 to 6)

wherein R^{351} represents hydrogen, C_{1-6} alkyl,

R^{352} represents hydrogen, C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsubstituted phenyl, benzoyl, C_{1-6} alkanoyl, phenylaminocarbonyl, phenylsulfonyl, or

R^{34} and R^{35} may form, together with the adjacent N atom, a 5 to 8 membered saturated heterocyclic ring, and said ring may be interrupted by NH, S or O atom and optionally substituted;

R^4 to R^6 are the same as R^1 to R^3 or the groups which can be reduced to R^1 to R^3;

E is carbamoyl, cyano, carboxyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbamoyl, nitro, C_{1-6} alkylsulfonyl, aryl sulfonyl, or arylcarbamoyl.

The term "aryl" used herein means aromatic moiety having 5 to 10 carbon atoms with one to two rings.

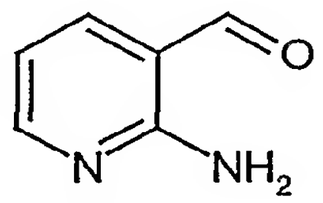
The term "heteroaryl" used herein means aromatic moiety having 2 to 9 carbon atoms with one to two rings and at least one heteroatom selected from the group consisting of oxygen, nitrogen and sulfur.

The term "C_{1-12} alkoxy" used herein means –O- straight or branched alkyl having 1 to 12 carbon atoms.

The reductant for the reduction of the naphthyridinone analogs is preferably hydrido complex, more preferably hydroborate, still more preferably tetrahydroborate, and most preferably sodium borohydride or lithium borohydride.

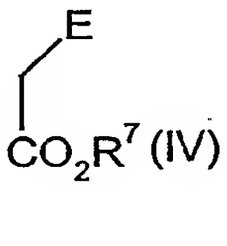
In case of hydrido complex is used, the reaction temperature is preferably -78°C to 40°C, more preferably -10°C to 25°C.

Preferably, the naphthyridinone analogs is prepared by the reaction of the compound containing the structure shown by following formula (III);



(III)

and the compound having the structure shown by the following formula (IV);



wherein R^7 is C_{1-6} alkyl.

The reaction of the compound (III) and (IV) is well known and can be performed in mild condition.

Typical salts of the compound shown by the formula (I),(II) and (III) include salts prepared by reaction of the compound of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively.

Acids to form acid addition salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, hydrochloric acid, hydrobromic acid, hydroiodic acid and the like.

Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tris(hydroxymethyl)-aminomethane, and the like. Examples of inorganic bases include, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

Examples of such salts are sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sevacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, γ-hydroxybutyrate, glycollate, tartarate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like salts of the compound of formula (I), (II) and (III). The preferred acid addition salts are those formed with mineral acids, such as, without limitation, hydrochloric acid, and hydrobromic acid, and those formed with organic acids, such as without limitation, maleic acid and methane-sulfonic acid. The potassium and sodium salt forms are particularly preferred base addition salts.

BEST MODE FOR CARRYING OUT THE INVENTION

In case of hydrido complex is used, the reduction of compound (II) can be carried out in a solvent including, for instance, ethers such as diethyl ether, tetrahydrofuran and dioxane; alcohols such as ethanol and methanol; nitriles such as acetonitrile; amides such as dimethylformamide; sulfoxides such as dimethyl sulfoxide, and others, or mixture thereof.

The reaction temperature can be optionally set depending on the compounds to be reacted. In case of sodium borohydride or lithium borohydride are used, the reaction temperature is usually, but not limited to, about -78°C to 40°C. It is preferably -10°C to 25°C. The reaction may be conducted for, usually, 5 min to 48 hours and preferably 30 min to 5 hours.

The reaction of compound (III) and (IV) is based on the reaction called "Friedlander quinoline synthesis". The reaction of compound (III) and (IV) can be induced in a solvent or without a solvent. The solvent, reaction temperature and reaction time can be optionally set depending on the compounds to be reacted.

The compounds of the general formula (III) and (IV) are commercially available, or can be prepared by the use of known techniques.

The compound (III) and compound (IV) can be heated under reflux to react for several hours in a solvent including. for instance. alcohols such as ethanol.ethers such as THF, dioxane; DMF, DMSO acetonitrile.and others or mixture thereof, and in the present of basic catalyst such as piperdine, NaOH or NaOEt.

In this reaction, the reaction temperature is usually about 30°C to the boiling point of the solvent, but not limited thereto. It is preferably the temperature of heating reflux.

In this reaction, the reaction time is usually 15 min to 30 hours, preferably 1 to 20 hours.

EXAMPLES

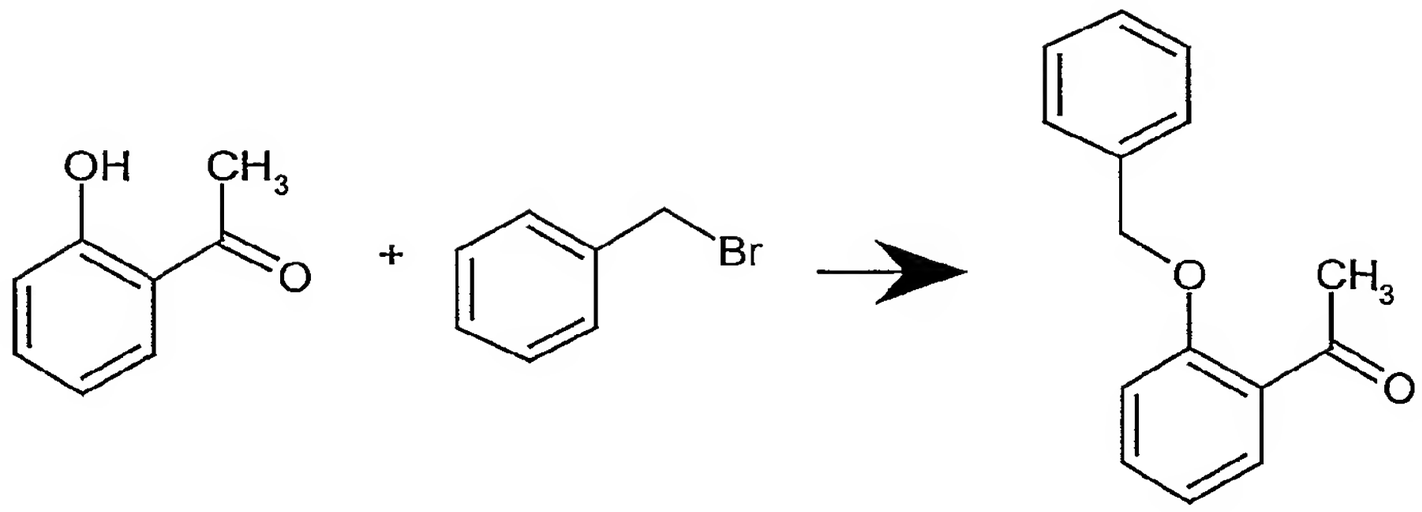
The present invention will be described in detail below in the form of examples, but they should by no means be construed as defining the metes and bounds of the present invention.

In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.

Melting points are uncorrected. ^1H NMR spectra were recorded using either Bruker DRX-300 (300MHz for ^1H) or 500 Bruker UltraShield™ (500MHz for ^1H) spectrometer in $CDCl_3$ or DMSO-d6. Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard at zero ppm. Coupling constant (J) are given in hertz and the abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet and multiplet, respectively. The abbreviation "br" refer to "broad ". Mass spectroscopy data were recorded on a FINNIGAN MAT 95. TLC was performed on a precoated silica gel plate (Merck silica gel 60 F-254). Silica gel (WAKO-gel C-200 (75-150μm))was used for all column chromatography separations. All chemicals were reagent grade and were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd., Tokyo kasei kogyo co. Ltd., Arch co-oporation.

Preparing method of starting compounds:

[Starting compound 1A]



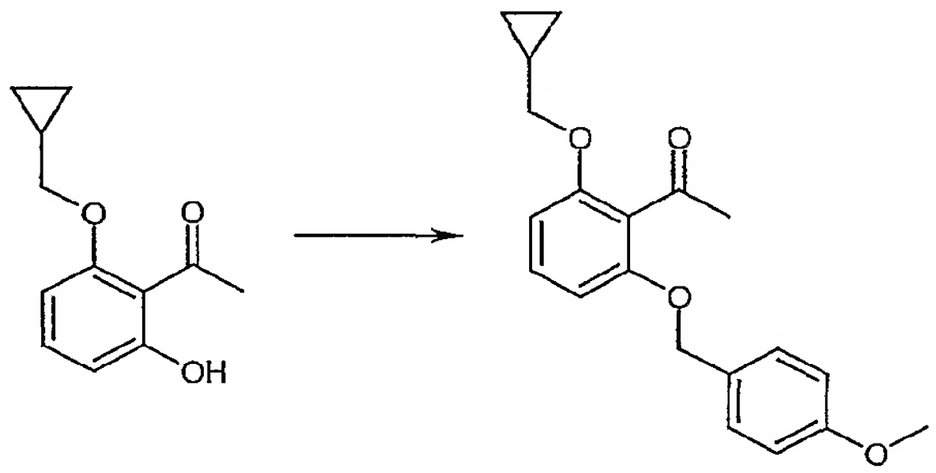
(Starting compound 1A)

A mixture of 2-hydroxyacetophenone (68.1g, 0.500mol), benzylbromide (65.4ml, 94.1g, 0.550mol) and K_2CO_3 (103g, 0.750mol) in acetone (1.00L) was heated to reflux. After overnight treatment, the volatiles were removed under reduced pressure to give a residue. The obtained residue was dissolved in the mixture of AcOEt and water. The resulting mixture was extracted with AcOEt. The extract was washed with brine, and dried over $MgSO_4$. After filtration, the volatile was removed under reduced pressure to give a crude material. The crude material was purified by distillation under reduced pressure to give a colorless oil. (100g, yield; 88%)

[Starting compound 1B]

To a stirred solution of 1-(2,6-dihydroxyphenyl)ethanone (50.0 g, 328 mmol) in acetone (1000 mL) were added potassium carbonate (227 g, 1643 mmol) and (bromomethyl)cyclopropane (35.1 mL, 361 mmol). The mixture was stirred at 50 °C for 2 days. The reaction mixture was filtrated on Celite®, and then the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The separated organic phase was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was suspended in hexane. Then the suspension was stirred at 80 °C for 30 min. The solution was filtered and the filtrate was allowed to cool to room temperature. The resulting white solid was collected by filtration, washed with hexane, and

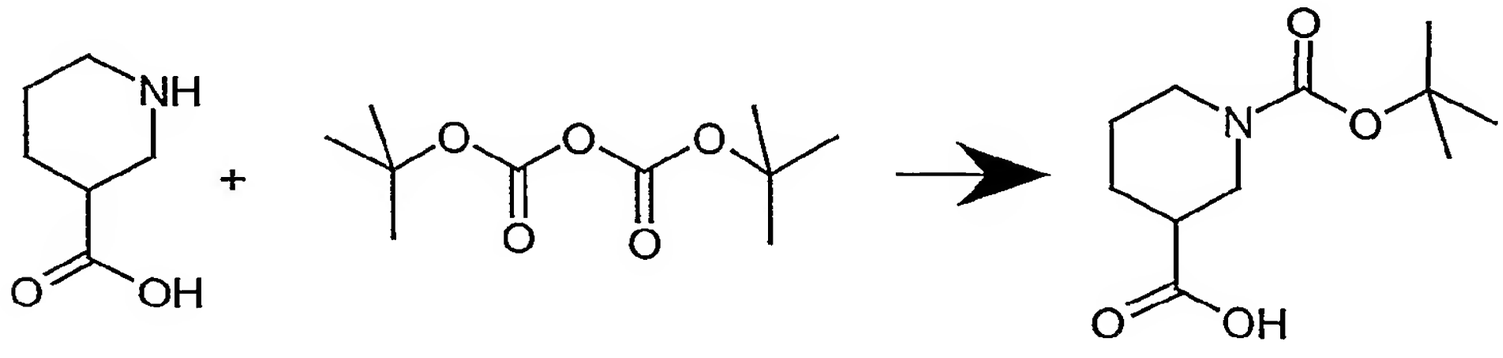
dried under reduced pressure to give 1-{2-[(cyclopropylmethyl)oxy]–6-hydroxy-phenyl}ethanone as a pale yellow solid (56.3 g, yield; 83%).



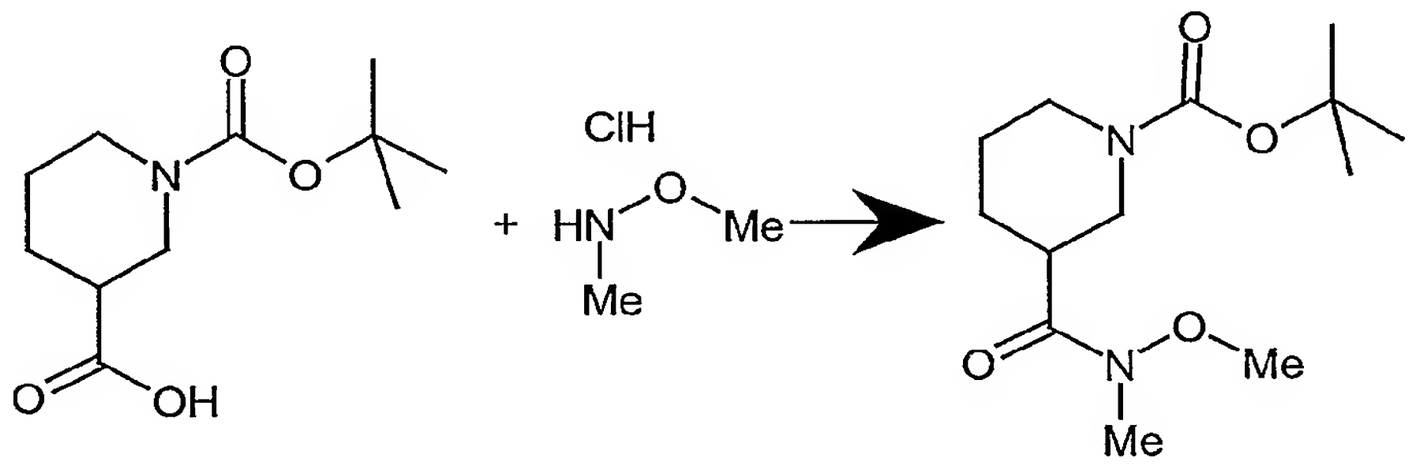
(Starting compound 1B)

To a stirred solution of 1-{2-[(cyclopropylmethyl)oxy]-6-hydroxyphenyl}ethanone (56.3 g, 272 mmol) in acetone (1000 mL) were added potassium carbonate (188 g, 1364 mmol), 4-methoxybenzyl chloride (40.9 mL, 300 mmol) and tetrabutyl-ammonium iodide (20.2 g, 54.6 mmol). The mixture was stirred at reflux overnight. The reaction mixture was allowed to cool to room temperature, filtered on Celite®, and then the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The separated organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Then the resulting white solid was recrystallized from ethanol, collected by filtration, washed with ethanol, and dried under reduced pressure to give 1-{2-(cyclo-propylmethoxy)-6-[(4-methoxybenzyl)oxy] phenyl}ethanone as a white solid (79.2 g, yield; 89%).

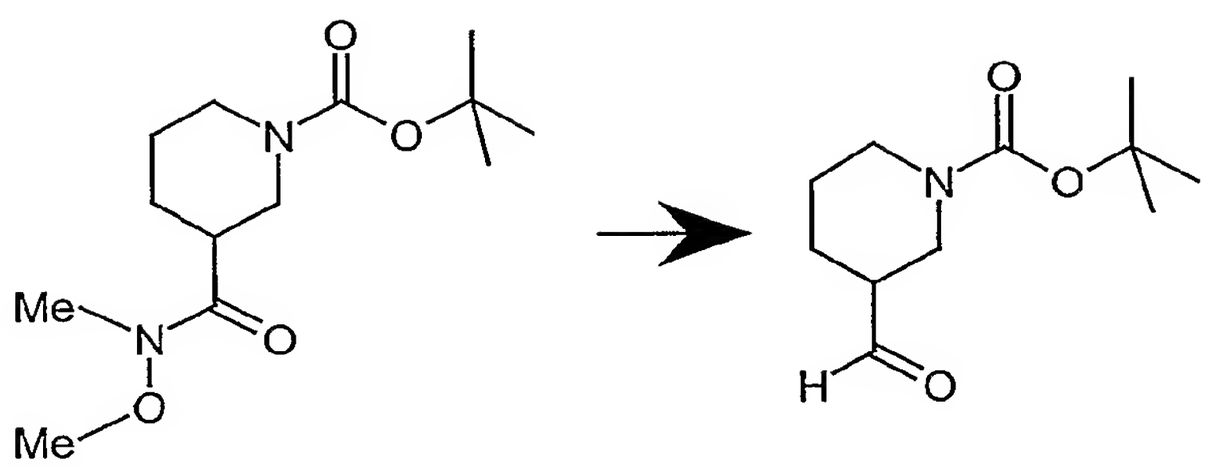
[Starting compound 2]



(1) To a cooled (0°C), stirred solution of 3-piperidinecarboxylic acid (100.000 g, 774.233 mmol) in dioxane (400 ml) were added 2N NaOH (400 ml, 800 mmol) and di-tert-butyl dicarbonate (168.978 g, 774.233 mmol). The mixture was stirred at 0°C – room temperature for 12 hrs. The mixture was concentrated in vacuo. The residue was diluted with water and acidified (pH 3-4) with aqueous 1N HCl solution. The resulting solid was collected by filtration. The white solid was dissolved in ethyl acetate/water and the organic layer was separated. The organic layer so obtained was dried over Na_2SO_4, filtered, and concentrated. The resulting solid was suspended in hexane and collected by filtration to give 1-(tert-butoxycarbonyl)-3-piperidine carboxylic acid as a white powder. (156 g, yield; 88%)



(2) To a stirred solution of 1-(tert-butoxycarbonyl)-3-piperidine carboxylic acid (7.000 g, 30.531 mmol) in dichloromethane (200 ml) was added triethylamine (4.681 ml, 33.584 mmol). After cooled to 0°C, benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (15.885 g, 30.531 mmol), N,O-dimethylhydroxy-amine (3.276 g, 33.584 mmol) and triethylamine (4.255 ml, 30.531 mmol), successively. The mixture was stirred at room temperature for 12 hrs. The reaction mixture was diluted with dichloromethane and washed with an aqueous 1N HCl solution, saturated aqueous $NaHCO_3$ solution, and brine, successively. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by silica gel column (chloroform/ethyl acetate = 10/1-9/1) to give tert-butyl 3-{[methoxy(methyl)amino]carbonyl}-1-piperidine-carboxylate as a white solid. (8.050g, yield;96%)

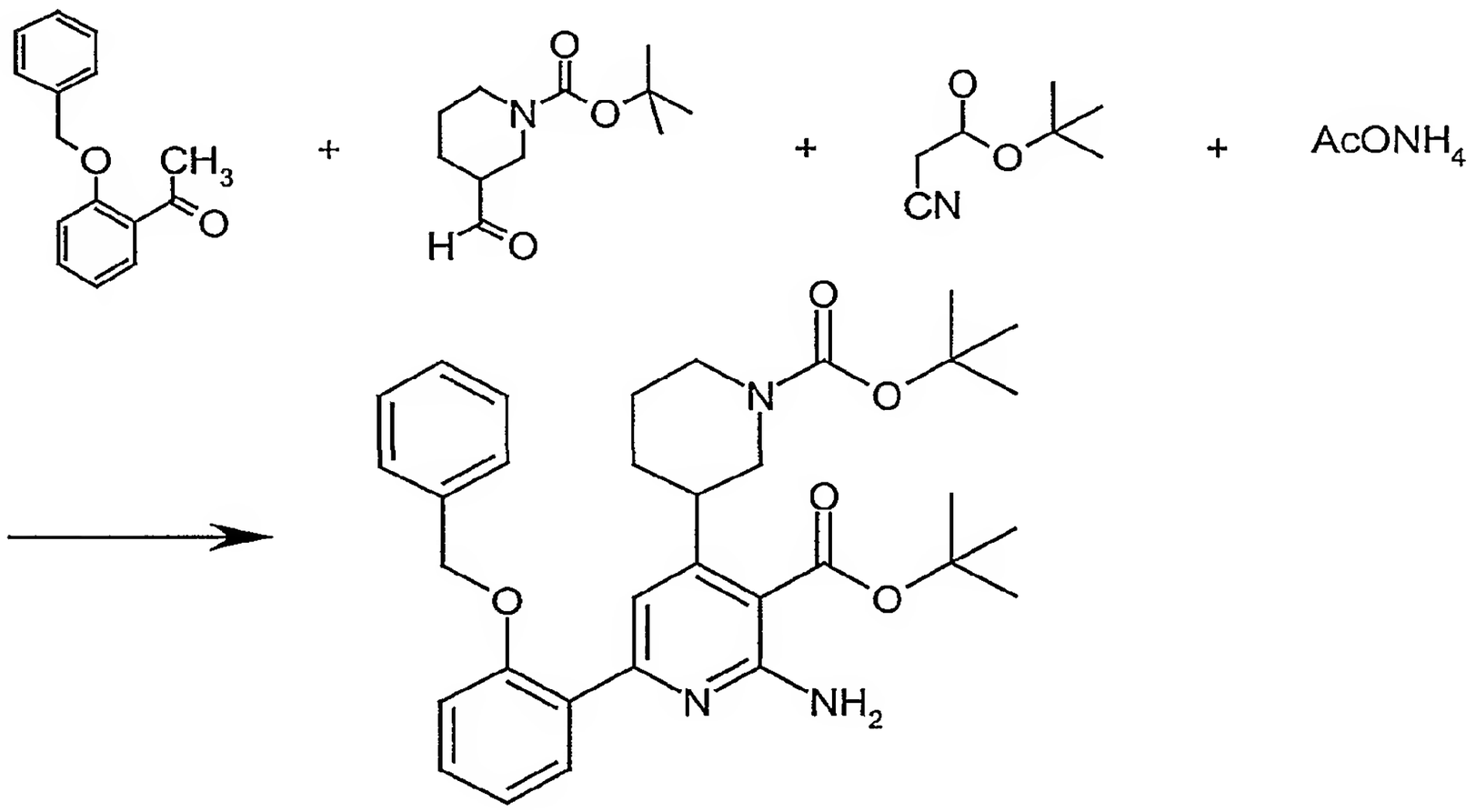


(Starting compound 2)

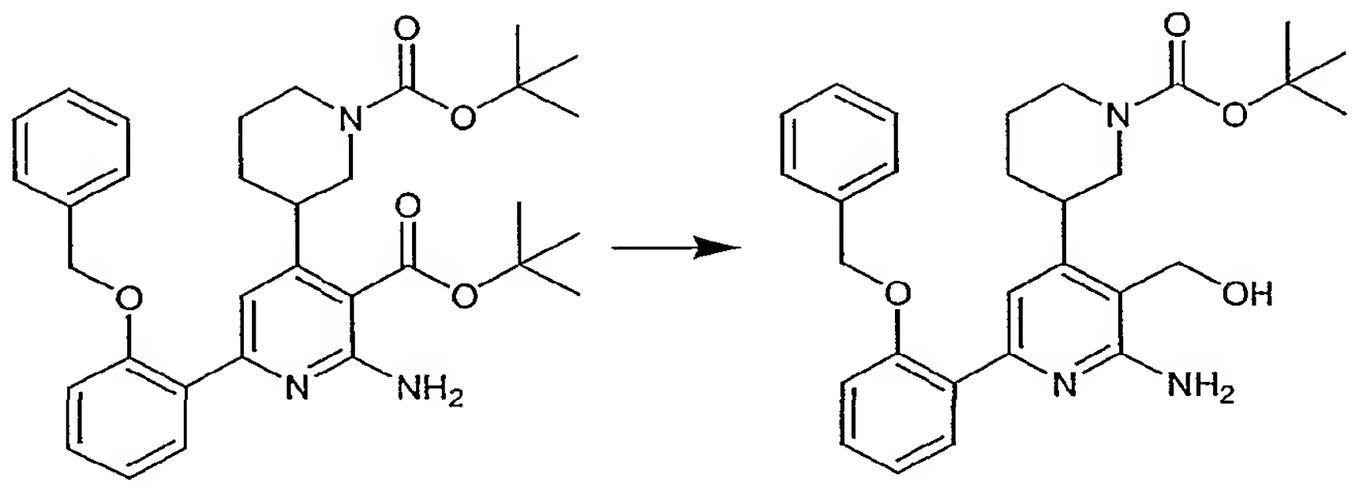
(3) To a cooled (-15°C), stirred suspension of lithium aluminum hydride (4.355 g, 114.743 mmol) in diethyl ether (500ml) was added tert-butyl 3-{[methoxy(methyl)amino]carbonyl}-1-piperidine-carboxylate (25.000 g, 91.795 mmol) in THF (150 ml) dropwise for 30 min. The reaction was quenched with aqueous 1N potassium hydrogen sulfate (300 ml). Then the resulting product was extracted with diethyl ether and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue (tert-butyl 3-formyl-1-piperidine carboxylate) was used for the next steps without further purification. (22.56 g, yield; about 100%)

Example 1:

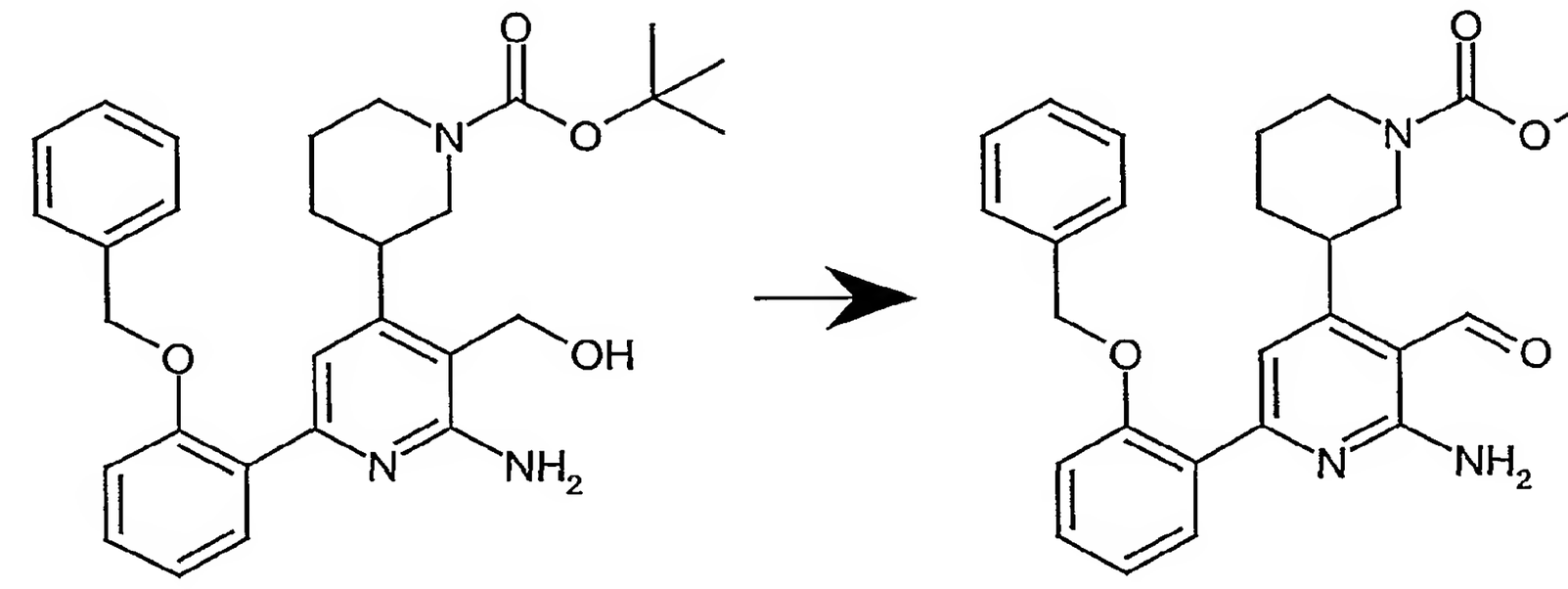
Ethyl 5-[1-(tert-butoxycarbonyl)-3-piperidinyl]-7-(2-hydroxy-phenyl)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate



(1) A mixture of 1-[2-(benzyloxy)phenyl]ethanone (3.50 g, 15.47 mmol) (starting compound 1A), *tert*-butyl 3-formyl-1-piperidinecarboxylate (3.30 g, 15.47 mmol) (Starting compound 2), *tert*-butyl cyanoacetate (2.18 g, 15.47 mmol), ammonium acetate (3.58 g, 46.40 mmol) and 1,2-dimethoxyethane (17 mL) was heated at reflux for 3.5 hrs. After cooled to room temperature, the mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane: ethyl acetate, 4:1) to give *tert*-butyl 2-amino-6-[2-(benzyloxy)phenyl]-4-[1-(*tert*-butoxycarbonyl)-3-piperidinyl]nicotinate (1.89 g, yield; 22%).

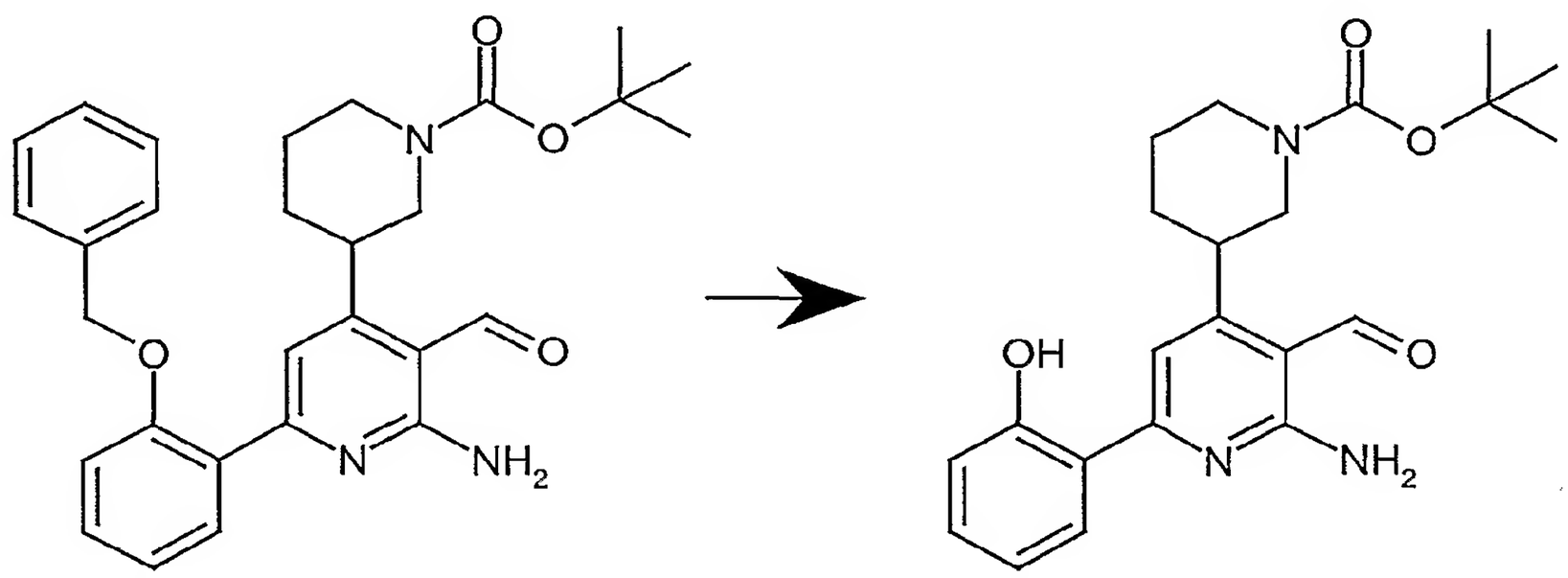


(2) To a cold (0°C) solution of *tert*-butyl 2-amino-6-[2-(benzyloxy)phenyl]-4-[1-(*tert*-butoxycarbonyl)-3-piperidinyl]nicotinate (2.590 g, 4.627 mmol) in THF (25 mL) was added $LiBH_4$ (0.202 g, 9.255 mmol). The mixture was allowed to warm to room temperature, and the stirring was continued for 5 hrs. The mixture was quenched with water, and extracted with ethyl acetate. The separated organic phase was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane: ethyl acetate, 2:3) to give *tert*-butyl 3-[2-amino-6-[2-(benzyloxy)phenyl]-3-(hydroxymethyl)-4-pyridinyl]-1-piperidinecarboxylate (0.904 g, yield; 40%).

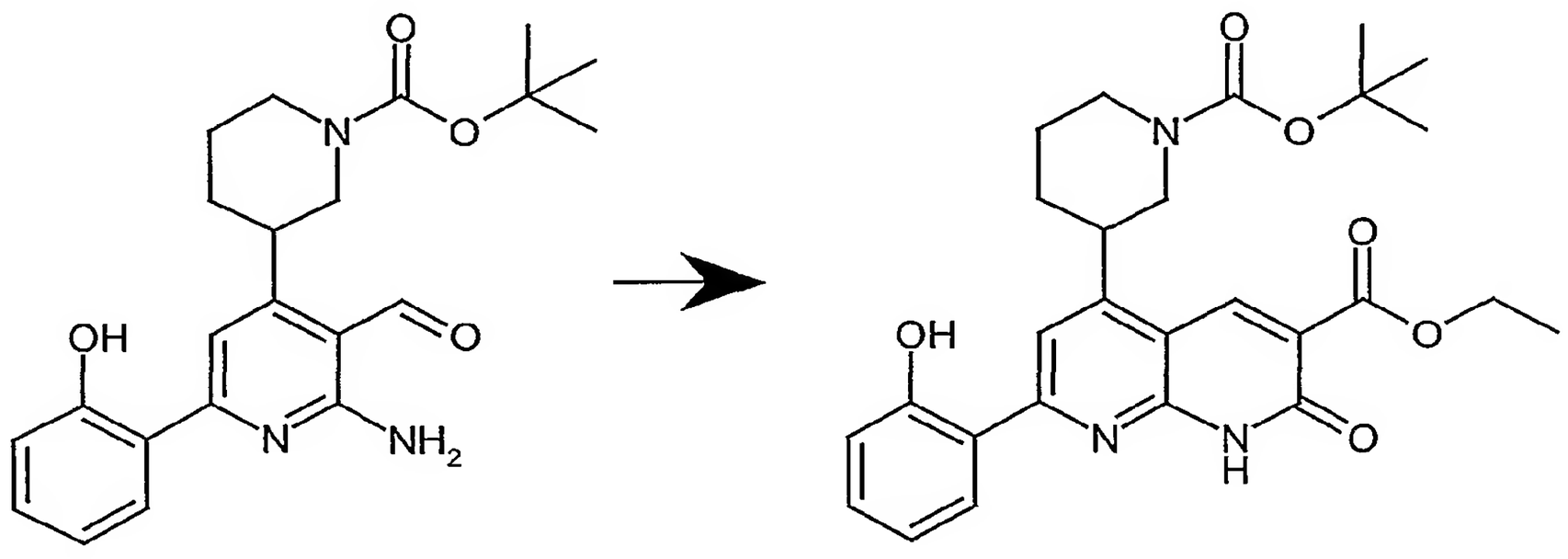


(3) To a solution of *tert*-butyl 3-[2-amino-6-[2-(benzyloxy)phenyl]-3-(hydroxymethyl)-4-pyridinyl]-1-piperidinecarboxylate (0.900 g, 1.838 mmol) in methylene chloride (20 mL) was added manganese (IV) oxide (3.20 g, 36.8 mmol). After stirred at room temperature for 40 min, the mixture was filtered to remove the

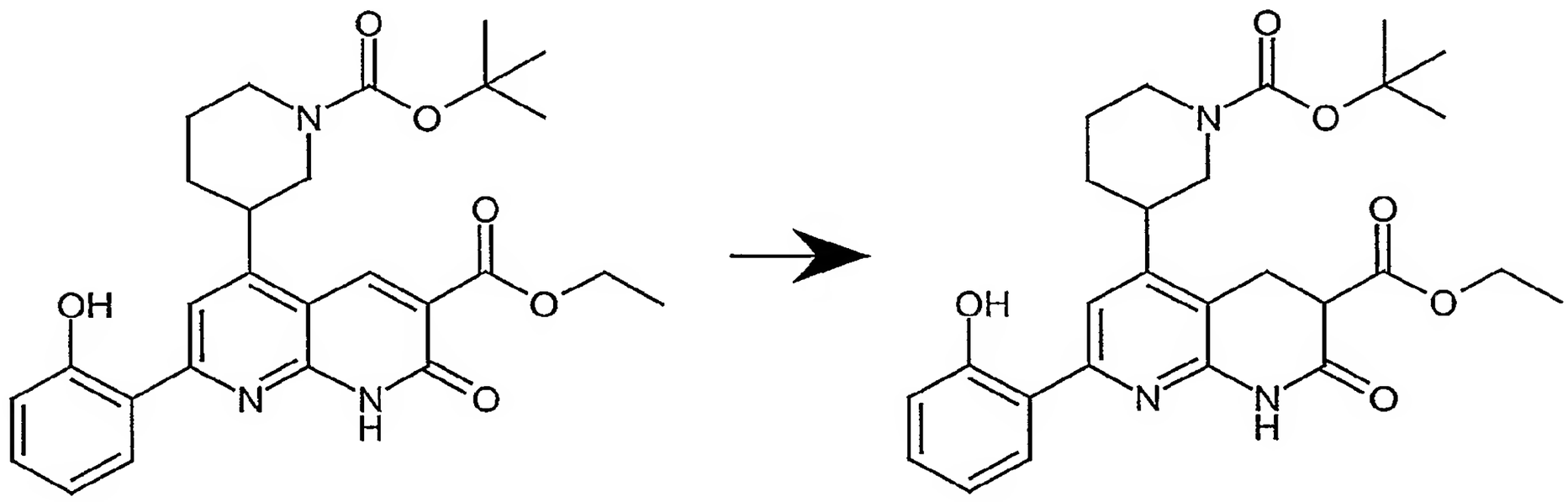
manganese salt. The filtrate was concentrated under reduced pressure. The resulting solid was purified by recrystallization from a mixture of ethyl acetate and hexane to give *tert*-butyl 3-[2-amino-6-[2-(benzyloxy)phenyl]-3-formyl-4-pyridinyl]-1-piperidinecarboxylate (0.651g, yield; 73%).



(4) A solution of *tert*-butyl 3-[2-amino-6-[2-(benzyloxy)phenyl]-3-formyl-4-pyridinyl]-1-piperidinecarboxylate (0.630 g, 1.29 mmol) in ethyl acetate (5.0 mL) and THF (11.0 mL) was hydrogenated at 1 atm in the presence of palladium on charcoal (10%, 0.30 g) overnight. The resulting mixture was filtered on Celite®, and washed with THF. The combined filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane: ethyl acetate, 2:1) to give *tert*-butyl 3-[2-amino-3-formyl-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (0.536 g, yield; quant.).



(5) To a suspension of *tert*-butyl 3-[2-amino-3-formyl-6-(2-hydroxyphenyl)-4-pyridinyl]-1-piperidinecarboxylate (0.86 g, 2.16 mmol) in ethyl alcohol (25 mL) were added diethyl malonate (6.93 g, 43.27 mmol) and piperidine (2.14 mL, 21.64 mmol) and , and the mixture was heated at reflux overnight. The mixture was allowed to cool to room temperature, and then diluted with ethyl alcohol. The resulting precipitate was collected by filtration, washed with ethyl alcohol and dried under reduced pressure to give ethyl 5-[1-(*tert*-butoxycarbonyl)-3-piperidinyl]-7-(2-hydroxyphenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate as a yellow solid (0.752 g, yield; 71%): LCMS (ES) *m/e* 494 $(M + H)^+$; ^1H NMR (300 MHz, DMSO-*d6*) δ 1.33 (3H, t, J = 6.9 Hz), 1.42 (9H, br s), 1.55 - 1.69 (1H, m), 1.70 - 1.81 (1H, m), 1.90 - 2.12 (2H, m), 2.75 - 3.01 (1H, m), 3.10 (1H, t, J = 12 Hz), 3.99 (2H, br), 4.30 (2H, q, J = 6.9 Hz), 6.92 - 7.05 (1H, m), 6.97 (1H, d, J = 7.9 Hz), 7.38 - 7.41 (1H, m), 7.92 (1H, s), 8.20 (1H, d, J = 7.9 Hz), 8.63 (1H, br), 12.75 (1H, br), 12.91 (1H, br).

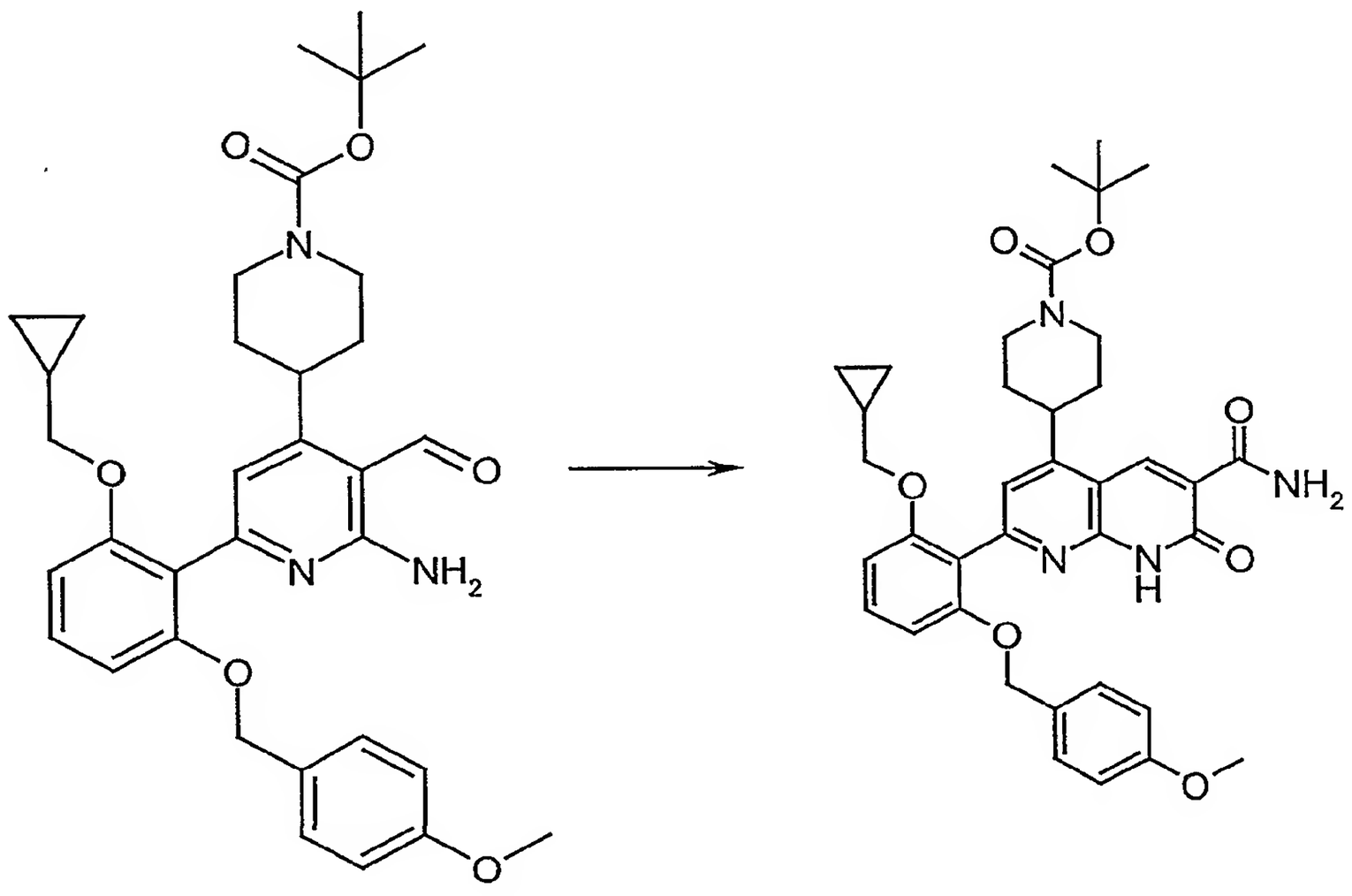


(6) To a cold (0°C) suspension of ethyl 5-[1-(*tert*-butoxycarbonyl)-3-piperidinyl]-7-(2-hydroxyphenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carboxylate (0.74 g, 1.49 mmol) in THF (20 mL) under an argon atmosphere was added $LiBH_4$ (0.065 g, 2.99 mmol). The mixture was allowed to warm to room temperature, and the stirring was continued for 3 hrs. The resulting mixture was quenched with water, and partitioned between ethyl acetate and a saturated ammonium chloride solution. The separated organic phase was washed with water and brine, dried over Na_2SO_4,

filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane: ethyl acetate, 2:1) to give Ethyl 5-[1-(*tert*-butoxycarbonyl)-3-piperidinyl]-7-(2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate as a white solid (0.475 g, yield; 64%): LCMS (ES) *m/e* 496 $(M + H)^+$; ^1H NMR (300 MHz, DMSO-*d6*) δ 1.16 and 1.17 (3H, t x 2, J = 7.2 Hz), 1.42 (9H, s), 1.40 - 1.60 (1H, m), 1.64 - 1.76 (1H, m), 1.82 - 1.98 (2H, m), 2.75 - 3.10 (4H, m), 3.75 - 3.84 (1H, m), 3.94 - 4.04 (2H, m), 4.13 (2H, q, J = 7.2 Hz), 6.88 - 6.91 (2H, m), 7.28 (1H, dd, J = 7.2, 7.9 Hz), 7.65 and 7.66 (1H, s x 2), 8.02 (1H, d, J = 7.9 Hz), 11.26 (1H, s), 12.59 (1H, s).

Example 2:

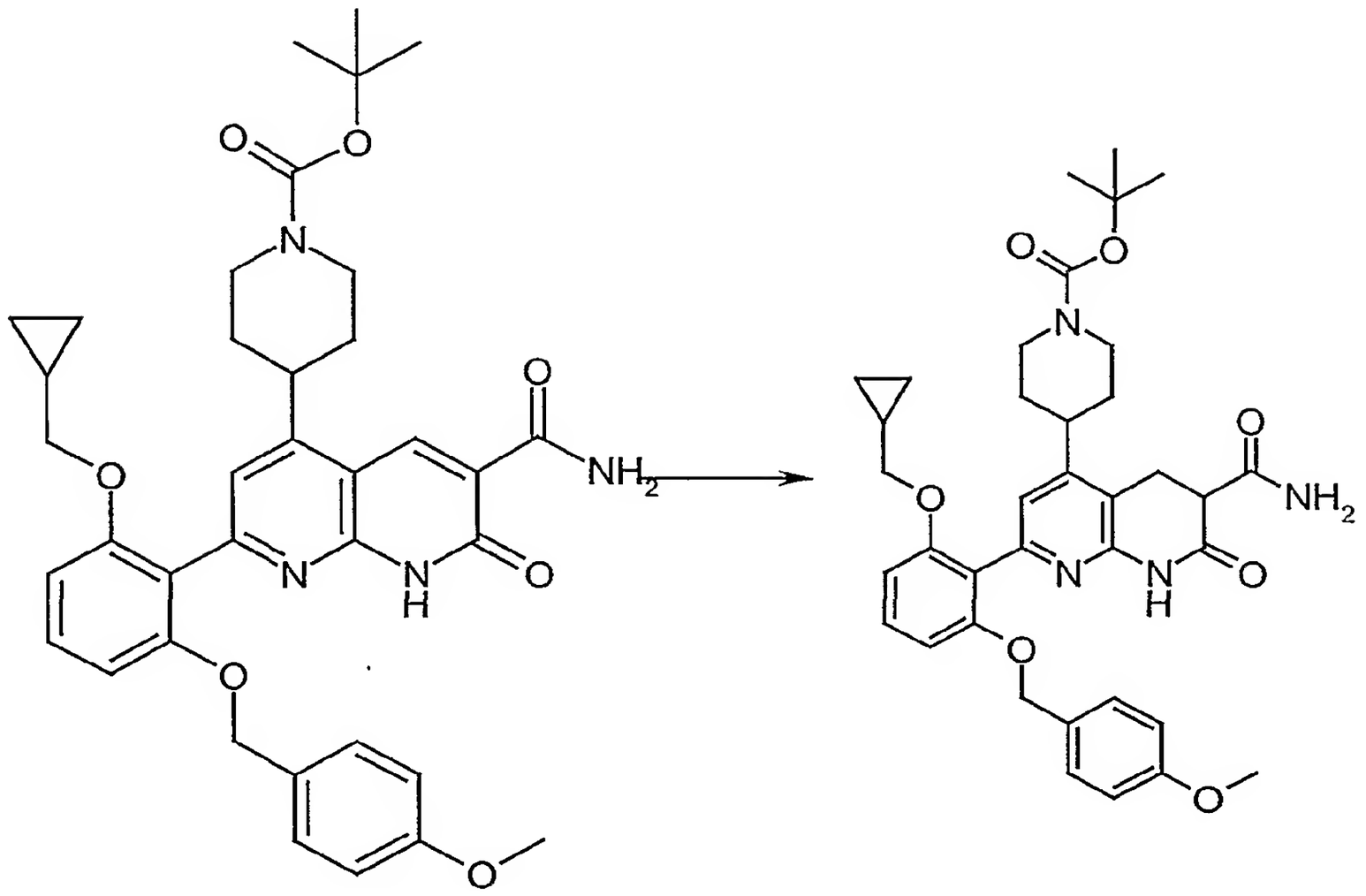
tert-butyl 4-(6-(aminocarbonyl)-2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-4-yl)-1 piperidinecarboxylate



(1) With the use of 1-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}ethanone (starting compound 1B) and *tert*-butyl 4-formyl-1-piperidinecarboxylate

(starting compound 2), *tert*-butyl 4-(2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3-formyl-4-pyridinyl)-1-piperidinecarboxylate was prepared in a similar manner as that of the steps (1)-(3) of Example 1.

To a solution of *tert*-butyl 4-(2-amino-6-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-3-formyl-4-pyridinyl)-1-piperidinecarboxylate (0.40 g, 0.68 mmol) in ethyl alcohol (5.0 mL) was added ethyl malonate monoamine (1.78 g, 13.61 mmol) and piperidine (0.58 g, 6.81 mmol). The mixture was refluxed for 12 hrs. After cooled to room temperature, the reaction mixture was partitioned between ethyl acetate and water. The separated organic phase was washed with saturated $NaHCO_3$ solution, water and brine successively, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane: ethyl acetate, 1:1 and then ethyl acetate) to give *tert*-butyl 4-(6-(aminocarbonyl)-2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-7-oxo-7,8-dihydro-1,8-naphthyridin-4-yl)-1-piperidinecarboxylate as a yellow form (0.455 g, yield; quant.): LCMS (ES) *m/e* 655 $(M + H)^+$; ^1H NMR (500 MHz, DMSO-*d6*) δ 0.15 - 0.18 (2H, m), 0.36 - 0.39 (2H, m), 0.96 - 1.05 (1H, m), 1.42 (9H, s), 1.51 - 1.67 (1H, m), 1.72 - 1.79 (2H, m), 2.99 (2H, br), 3.50 - 3.58 (1H, m), 3.70 (3H, s), 3.80 (2H, d, J = 6.6 Hz), 4.10 (2H, br), 4.98 (2H, s), 6.74 (1H, d, J = 8.5 Hz), 6.80 - 6.84 (3H, m), 7.18 (1H, s), 7.23 (2H, d, J = 8.8 Hz), 7.34 (1H, dd, J = 8.2, 8.5 Hz), 7.82 (1H, s), 9.00 (1H, s), 9.08 (1H, br), 12.75 (1H, br).



(2) To a cold (0 °C) solution of 4-(6-(aminocarbonyl)-2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-7-oxo-7,8-dihydro-1,8-naphthyridin-4-yl)-1-piperidinecarboxylate (0.200 g, 0.305 mmol) in methyl alcohol (5.0 mL) under an argon atmosphere was added $NaBH_4$ (0.010 g, 0.367 mmol). The mixture was allowed to warm to room temperature, and the stirring was continued for 12 hrs. The reaction mixture was quenched with water, and extracted with ethyl acetate. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give *tert*-butyl 4-(6-(aminocarbonyl)-2-{2-(cyclopropylmethoxy)-6-[(4-methoxybenzyl)oxy]phenyl}-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-4-yl)-1 piperidinecarboxylate (0.133 g, yield; 67 %): LCMS (ES) *m/e* 657 $(M + H)^+$; ^1H NMR (500 MHz, DMSO-*d6*) δ 0.15 - 0.19 (2H, m), 0.38 - 0.41 (2H, m), 1.00 - 1.08 (1H, m), 1.40 (9H, s), 1.41 - 1.53 (1H, m), 1.66 - 1.71 (2H, m), 2.88 (2H, br), 2.99 - 3.07 (1H, m), 3.13 (1H, d, J = 8.5 Hz), 3.41 - 3.44 (1H, m), 3.72 (3H, s), 3.77 (2H, dd, J = 2.8, 6.6 Hz), 4.01 - 4.12 (2H, m), 4.95 (2H, s), 6.69 (1H, d, J = 8.5 Hz), 6.77 (1H, d, J = 8.2 Hz), 6.81 (1H, s), 6.85 (2H, d, J = 8.8 Hz), 7.16 (1H, s), 7.22 (2H, d, J = 8.8 Hz), 7.24 (1H, dd, J = 8.2, 8.5 Hz), 7.47 (1H, s), 10.50 (1H, s).

Other 3,4-dihydro naphthyridinone analogs could be prepared by the similar procedure.

INDUSTRIAL APPLICABILITY

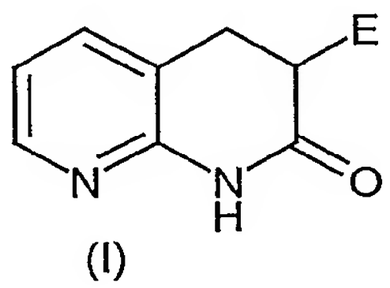
The novel synthetic method of 3,4-dihydro naphthyridinone analogs is provided by this invention.

By using naphthyridinone analogs with a electrowithdrawing group in 3-position as the precursor of corresponding 3,4-dihydro naphthyridinone, the 3,4-dihydro naphthyridinone can be prepared easily under mild condition and various substituent can be introduced.

3,4-dihydro naphthyridinone analogs and salts thereof would be useful template for biologically active compounds, e.g. pyridine derivatives which inhibit IκB kinase β (IKK-β or IKK-beta) activity, thus inhibit nuclear factor kappa B (NF-κB) activity, and can be used for the prophylaxis and treatment of diseases associated with NF-κB activity, in particular for the treatment of inflammatory diseases.

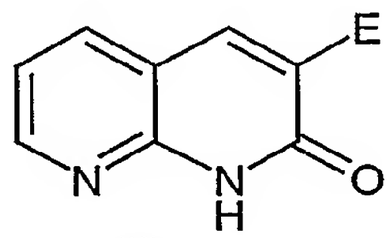
CLAIMS:

1. A process for producing 3,4-dihydro naphthyridinone analogs and salts thereof containing the structure shown by the following structural formula (I);



(I)

comprising the reduction of naphthyridinone analogs containing the structure shown by the following structural formula (II);

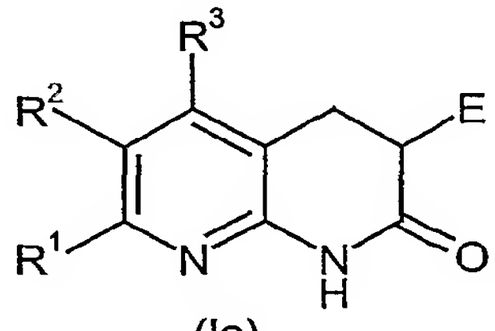


(II)

wherein E is an electrowithdrawing group.

2. The process as claimed in claim 1, wherein E is carbamoyl, cyano, carboxyl, C_{1-6} alkoxycarbonyl, C_{1-6}alkylcarbamoyl, nitro,C_{1-6}alkylsulfonyl, aryl sulfonyl, or arylcarbamoyl.

3. The process as claimed in claim 1, wherein the structure of the 3,4-dihydro naphthyridinone analogs is shown by the following structural formula (Ia);

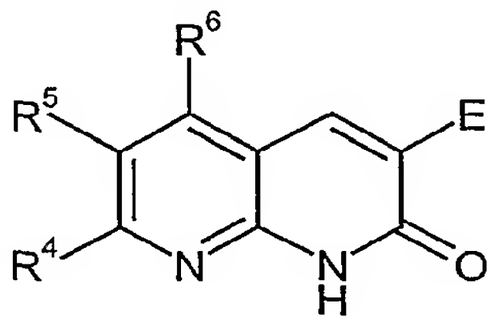


(Ia)

wherein:

R^1 , R^2 and R^3 are different or identical and represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, carboxyl, halogen, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, halogen substituted alkyl, nitro, cyano, hydroxy, aryl, heteroaryl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{3-8} cyclo-alkylamino, benzylamino, carbamoyl, -O-C_{1-6} alkylene-phenyl, -O-phenyl, styryl or 1,2,3,6-tetrahydro-pyridine, and optionally substituted by one or more substituents;

and the structure of the naphthyridinone analogs are shown by the following structural formula (IIa);

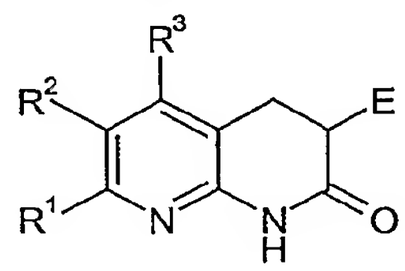


(IIa)

wherein R^4 to R^6 are the same as R^1 to R^3 or the groups which can be reduced to R^1 to R^3;

E is carbamoyl, cyano, carboxyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbamoyl, nitro, C_{1-6} alkylsulfonyl, aryl sulfonyl, or arylcarbamoyl.

4. The process as claimed in claim 1, wherein the structure of the 3,4-dihydro naphthyridinone analogs is shown by the following structural formula (Ia);



(Ia)

wherein:

R^1 is hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, carboxyl, halogen, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, halogen substituted alkyl, nitro, cyano, hydroxy, phenyl, 2-pyridil, 3-pyridil, 4-pyridil, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, amino, C_{1-6} alkylamino, C_{3-8} cycloalkylamino, benzylamino, carbamoyl, -O-C_{1-6} alkylene-phenyl, or -O-phenyl, and R^1 is optionally substituted by one or more substituents,

wherein the optional substituents are each independently hydrogen, C_{1-6} alkyl, halogen, hydroxy, C_{1-12} alkoxy, nitro, amino, C_{1-6} alkylsulfonylamino, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, di (C_{1-6} alkyl)amino, C_{1-6} alkanoylamino, phenyl C_{1-6} alkylamino, phenylsulfonylamino, or -O-$(CH_2)_n$-R^{11} ,

wherein n represents an integer selected from 0 to 6, and R^{11} is C_{2-6} alkenyl, benzoyl, diphenylmethyl, di (C_{1-6} alkyl)amino, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, or a 3 to 10 membered saturated or unsaturated ring having 0 to 3 heteroatoms selected from the group consisting of S, O and N as heteroatoms and is optionally substituted by C_{1-6} alkyl, mono or di halogen, halogen substituted C_{1-6} alkyl, nitro, ciano, C_{1-6} alkoxycarbonyl, phenyl, hydroxy, amino, C_{1-6} alkylamino, di (C_{1-6} alkyl)amino, C_{1-6} alkanoylamino, C_{1-6} alkoxy, or carbamoyl;

R^2 is hydrogen, hydroxy, halogen, or C_{1-6} alkyl;

R^3 is 1,2,3,6-tetrahydro-pyridine, optionally substituted phenyl or styryl;

wherein the optional substituents are each independently hydrogen, halogen, amino, C_{1-6} alkoxy, di C_{1-6} alkylamino, C_{1-6} alkanoylamino, C_{1-6} alkyl(hydroxy C_{1-6} alkyl)amino, C_{1-6} alkyl(benzyl)amino, morpholino, optional-

ly substituted piperidino, or optionally substituted pyrrolidino, C_{1-6} alkylsulfonylamino, piperidino-C_{1-6} alkylene-oxy, -CO-NHR^{51}, or –NH-COR^{51},

wherein R^{51} represents piperidino-C_{1-6} alkylene, carboxy-C_{1-6} alkylene, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy-C_{1-6} alkylene, oxotetrahydrofuryl, oxopyrrolidinyl, -CH(OH)R^{51a}, -CH(NH_2)R^{51b}, -C_{1-6} alkylene-R^{51c},

wherein R^{51a} is carboxy-C_{1-6} alkylene or C_{1-6} alkoxycarbonyl-C_{1-6} alkylene,

R^{51b} is C_{1-6} alkyl, or carboxy-C_{1-6} alkylene,

R^{51c} is optionally substituted piperidino, optionally substituted piperazino, optionally substituted amino, or -CH(NH_2)-carboxy;

$$-CR^{31}R^{32}R^{33},$$

wherein R^{31} is hydrogen or C_{1-6} alkyl,

R^{32} is hydrogen, α-aminobenzyl, a 5 to 8 membered saturated ring having 0 to 3 atoms selected from the group consisting of S, O and N as heteroatoms, or optionally substituted C_{1-6} alkyl, and

R^{33} is hydrogen, amino, C_{1-6} alkoxycarbonylamino, C_{2-6} alkenyloxycarbonylamino, piperidino-C_{1-6} alkylcarbonylamino, or 9-fluorenyloxycarbonylamino or

R^{32} and R^{33} may form, together with the adjacent carbon atom, an optionally substituted or optionally benzene fused 5 to 8 membered saturated ring having 0 to 3 heteroatoms selected from the group consisting of N, O and S as heteroatoms;

$-NR^{34}R^{35}$,

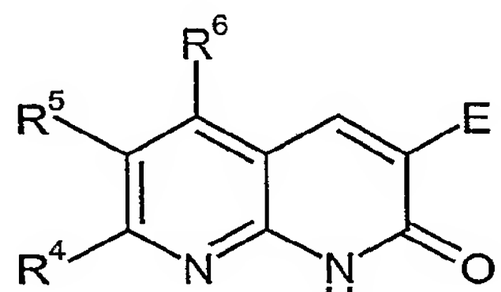
wherein R^{34} is hydrogen or C_{1-6} alkyl and R^{35} is hydrogen, C_{1-6} alkyl, or a 5 to 8 membered saturated ring having 0 to 3 heteroatoms selected from the group consisting of N, O and S as heteroatoms, or $-(CH_2)_m-NR^{351}R^{352}$(m represents any of integers from 1 to 6)

wherein R^{351} represents hydrogen, C_{1-6} alkyl,

R^{352} represents hydrogen, C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsubstituted phenyl, benzoyl, C_{1-6} alkanoyl, phenylaminocarbonyl, phenyl-sulfonyl, or

R^{34} and R^{35} may form, together with the adjacent N atom, a 5 to 8 membered saturated heterocyclic ring, and said ring may be interrupted by NH, S or O atom and optionally substituted;

and the structure of the naphthyridinone analogs are shown by the following structural formula (IIa);



(IIa)

wherein R^4 to R^6 are the same as R^1 to R^3 or the groups which can be reduced to R^1 to R^3;

E is carbamoyl, cyano, carboxyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylcarbamoyl, nitro, C_{1-6} alkylsulfonyl, aryl sulfonyl, or arylcarbamoyl.

5. The process as claimed in claim 1, wherein the reductant is hydrido complex.

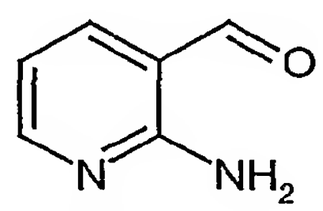
6. The process as claimed in claim 1, wherein the reductant is hydroborate.

7. The process as claimed in claim 1, wherein the reductant is tetrahydroborate.

8. The process as claimed in claim 1, wherein the reductant is sodium borohydride or lithium borohydride.

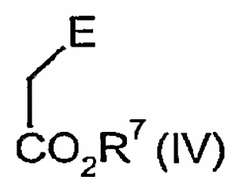
9. The process as claimed in any one of claim 5 to 8, wherein the reaction temperature is -78°C to 40°C.

10. The process as claimed in claim 1, wherein the naphthyridinone analogs is prepared by the reaction of the compound containing the structure shown by following formula (III);



(III)

and the compound having the structure shown by the following formula (IV);



(IV)

wherein R^7 is C_{1-6} alkyl.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/EP 01/10462

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SINGH B ET AL: "NOVEL CAMP PDE III INHIBITORS: IMIDAZO4,5-BPYRIDIN-2(3H)-ONES ANDTHIAZOLO4,5-BPYRIDIN-2(3H)-ONES AND THEIR ANALOGS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 37, 7 January 1994 (1994-01-07), pages 248-254, XP000925892 ISSN: 0022-2623 compounds 22 and 28 ---	1-10
A,P	WO 01 27103 A (SMITHKLINE BEECHAM CORP ;NEWLANDER KENNETH A (US); JAKAS DALIA R () 19 April 2001 (2001-04-19) cited in the application the whole document -----	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2002	30/01/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bosma, P

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INTERNATIONAL SEARCH REPORT

ormation on patent family members

Inte nal Application No
PCT/EP 01/10462

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0127103 A	19-04-2001	AU 7874700 A	23-04-2001
		WO 0127103 A1	19-04-2001